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Do Pharmacotherapy and/or Psychotherapy Work in Depression? It Depends!

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The answer to whether treatments like pharmacotherapy and psychotherapy ameliorate a given disorder (e.g. depression) may strongly impact patients, treatment decisions and health care expenditures. After their reanalysis of previous meta-analyses and the large STAR*D study, Pigott et al. [1] concluded that antidepressants were 'only marginally efficacious' (p. 267) compared to placebo. Given that 'it is unlikely that a syndrome as polymorphic and widely diagnosed as major depressive disorder (MDD) will reflect a single process' [2, p.131], the present statement will inquire about the conclusions to be drawn from the data of Pigott et al., while neglecting the typical methodological critique of specific meta-analyses (e.g. study selection, data analysis, etc.) and assuming accuracy in their main finding.

Results from meta-analyses essentially present weighted averages of average effect sizes per study [3]. Conclusions based on meta-analyses tend to be generalized across depressive patients varying in sex, age, family status, illness characteristics, comorbidity and (duration of) prior treatment, as well as across studies differing both in methodology and analysis of influential factors (e.g. agents affecting different biochemical pathways). However, there is compelling evidence indicating that these and other factors can modify causal treatment effects [e.g. 4]. A marginal overall effect in combination with considerable effect modification would still suggest that some patients experience strong positive effects after being administered an antidepressant.

Recent conceptual work [5] has shown how a better grounding of scientific analyses on the definition of 'causal effects' can counteract potential overgeneralization, which is known as one of the main pitfalls of meta-analyses. In the proposed counterfactual model, a causal effect of a particular treatment (e.g. antidepressant intervention) is defined to be present if a particular person shows a different outcome after treatment than if the same person had been assigned to another condition (e.g. wait list) at the time of the treatment decision. Hence, antidepressant effects are considered to vary across individuals and time (in addition to out-

come). This local understanding of causal effects prevents an a priori clustering of factors that could modify the effect of the intervention, as well as a drawing of global conclusions without examining the most striking potential effect modifiers. The analyses of Pigott et al. [1] represent an extraordinary strength by combining a meta-analytic strategy with an analysis of a large original study that takes different stages of depression treatment into account. Nevertheless, the authors continue to aggregate across all other factors.

Conversely, clinical wisdom and more sophisticated treatment models [e.g. 6] follow the logic of 'adaptive indication' implicitly taking effect modifiers into account. This does not apply to antidepressants alone. Suppose a patient who contacts a general practitioner: regardless of the question the patient may pose (e.g. 'Do marathons hurt my knees?' or 'Should I take antidepressants?'), the practitioner would wisely consider the potential effect modifiers (e.g. the patient's condition, including treatment history or preference). Rather than responding with a dichotomous 'yes' or 'no', the practitioner would provide the best empirically informed answer by stating: 'It depends!' Future research should tell us more precisely on what.

References

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